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Required ozone doses for removing pharmaceuticals from wastewater effluents

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Abstract The aim of the thisstudy was to investigate the ozone dosage required to remove active pharmaceutical ingredients (APIs) from biologically treated wastewater of varying quality, originated from different raw wastewater and wastewater treatment processes.

Secondary effluents from six Swedish wastewater treatment plants (WWTP) were spiked with 42 APIs (nominal concentration 1μg/L) and treated with different O_3 doses (0.5-12.0 mg/L ozone) in bench-scale experiments.

In order to compare the sensitivity of APIs in each matrix, the specific dose of ozone required to achieve reduction by one decade of each investigated API (DDO_3) was determined for each effluent by fitting a first order equation to the remaining concentration of API at each applied ozone dose. Ozone dose requirements were found to vary significantly between effluents depending on their matrix characteristics.

The specific ozone dose was then normalized to the dissolved organic carbon (DOC) of each effluent. The DDO_3/DOC ratios were comparable for each API between the effluents.

15 of the 42 investigated APIs could be classified as easily degradable ($DDO_3/DOC \leq 0.7$), while 19 were moderately degradable ($0.7 < DDO_3/DOC \leq 1.4$), and 8 were recalcitrant towards O_3-treatment ($DDO_3/DOC > 1.4$). Furthermore, we predict that a reasonable estimate of the ozone dose required to remove any of the investigated APIs may be attained by multiplying the experimental average DDO_3/DOC obtained with the actual DOC of any effluent.

Keywords: matrix effect; ozonation; ozone dose, pharmaceuticals; wastewater.

1. Introduction

The modern life-style of developed countries involves daily usage of artificial compounds such as active pharmaceutical ingredients (API), personal care products, hormones, pesticides and other environmentally persistent chemicals. As a result residues of these compounds become micropollutants in wastewater (Fick et al., 2010; Hollender et al., 2009; Richardson, 2010; Gerrity and Snyder, 2011; Huber et al., 2005; Richardson, 2010). Of all groups of micropollutants the vast majority of research activities are currently focused on the fate of active pharmaceutical ingredients during wastewater treatments (Hollender et al., 2009; Huber et al., 2003; Huber et al., 2005; Lee and von Gunten, 2010; Zimmermann et al., 2011; Fick et al., 2011; Falås et al., 2012a, 2012b). APIs by purpose are generally designed to illicit a specific biological action. Due to their use pattern, release to the environment is mainly via sewage outlets into surface waters. APIs are usually found at concentrations ranging from pg/L- µg/L in wastewater and surface waters influenced by wastewater outlets. However, chronic exposure of APIs to humans and wildlife even at these low concentrations is both of scientific and societal concern (Richardson, 2010).

To address this problem many WWTPs consider incorporating an additional treatment process step to remove APIs from the effluent. Treatment with O_3 appears to be one of the most promising technologies for the removal of these compounds (Ternes et al., 2003. Hansen et al., 2010; Hollender et al., 2009; Huber et al., 2003; Huber et al., 2005; Lee and von Gunten, 2010; Zimmermann et al., 2011).

One of the first studies which showed the efficiency of ozonation for removal of micropollutants in biological treated wastewater was by Ternes et al. (2003). Ozonation was employed at 5.0 to 15.0 mg/L of O_3 to investigate the removal efficiency (Ternes et al., 2003) for selected APIs, personal care products and iodated X-ray contrast media. Pharmaceuticals and personal care products were removed sufficiently by only 5 mg/L of O_3 while the iodated X-ray contrast media were only partially removed by 15 mg/L of O_3. However, as there is not much toxicological concern for iodated X-ray contrast media results were interpreted as promising and more optimised treatment studies were conducted which reported efficient removal of pharmaceuticals and hormones in wastewater at lower O_3 doses (2.0-3.5 mg/L) (Bahr et al., 2007; Hansen et al., 2010; Huber et al., 2005). Estimating the removal efficiencies of APIs from wastewater effluents in bench and pilot scale experiments, was the main focus of subsequent studies (Hollender et al., 2009; Huber et al., 2003; Zimmermann et al., 2011). For example, Hollender et al. (2009) studied the removal efficiencies of 220 pharmaceuticals in full scale with conventional activated sludge sewage treatment followed

by ozonation and sand filtration. Kinetic studies and modeling of ozonation based on reactor hydraulics, O_3 chemistry and reaction kinetics were also performed for a full scale municipal wastewater facility (Zimmermann et al., 2011).

Generally, APIs and other micropollutants are easy to degrade, i.e. can be removed with low ozone dosage, if they react reasonable fast with molecular ozone. If a micropollutant does not react well with ozone it will still degrade with higher applied ozone dosage via a secondary oxidation mechanism by which O_3 in water is converted to the hydroxyl radical, $HO^{\bullet}$, which is very reactive (non-selective) to most organic molecules.

Up to now, the parameter most commonly used by researchers to determine how well an API reacts with O_3, is the second order rate constant with O_3 ($k_{O3,API}$, selective oxidation) and $HO^{\bullet}$ ($k_{HO,API}$, non-selective oxidation) (Hollender et al., 2009; Huber et al., 2003; Zimmermann et al., 2011). According to these studies, compounds with $k_{O3,API}$ greater than 10^4 $M^{-1}s^{-1}$, require low delivered O_3 doses (easily degraded). Compounds with $k_{O3,API} < 10^4$ $M^{-1}s^{-1}$, are more persistent to O_3 treatment and therefore their degradation occurs mainly via reaction with $HO^{\bullet}$, the secondary degradation route of ozonation.

However, of the several hundred APIs which have been detected in WWTP effluents (Ternes et al., 1998; Kolpin et al., 2002; Hollender et al., 2009; Fick et al., 2011; Falås et al., 2012) very few have had their respective $k_{O3,API}$ and $k_{HO\bullet,API}$ determined (Benner and Ternes, 2009; Buffle et al., 2006a; Dodd et al., 2006; Huber et al., 2003; Huerta-Fontela et al., 2011). In fact, constants are available for less than 10% of the model APIs used in this study (Table S2). Even when these two rate constants ($k_{O3,API}$ and $k_{HO,API}$) are known for an API, an experiment to determine the ozone and HO exposure that results from an ozone dose in the specific wastewater is needed before the degradation of the API can be predicted (Huber et al., 2005; Buffle et al., 2006b).

With O_3 production being an energy intensive process (Kim and Tanaka, 2011), it is important for WWTPs to use optimum O_3 doses that achieve sufficient API degradation while maintaining low operational cost (Bahr et al., 2007; Hansen et al., 2010). APIs exhibit different susceptibilities to O_3 degradation which can vary up to 10 orders of magnitude (Hoigne and Bader, 1983; Hollender et al., 2009; Huber et al., 2003). They are also competing for O_3 degradation with the organic components found in the matrix of the WWTP effluent (Hollender et al., 2009) that vary in amount and quality depending on the treatment process and origin of wastewater. This makes it particularly difficult to predict the required

O_3 dosage requirements (DO_3) for satisfactory API removal in WWTP effluents, which is a crucial parameter in estimating treatment design and therefore cost.

Therefore, this study aimed to unveil a more direct approach to describe the removal of pharmaceuticals in wastewater effluents, which could also be used to predict the required O_3 dose for 90% removal of a specific pharmaceutical in a wastewater, solonly based on simple water quality parameters. To achieve this, the required delivered O_3 dose (0.5 mg/L ≤ DO_3 ≤ ~12 mg/L) to achieve one order of magnitude removal of 42 APIs (at low concentrations, μg/L, Table S2) from 6 Swedish WWTP effluents, were investigated. These APIs are commonly found in the WWTP effluents of Sweden (Fick et al., 2011, 2012; Falås et al., 2012a) and have different susceptibilities to ozonation (Benner and Ternes, 2009; Buffle et al., 2006a; Dodd et al., 2006; Hoigne and Bader, 1983; Huber et al., 2003).

Effluents used in the experiments were chosen to represent typical variations observed in the main traditional characteristics of effluent quality that would occur due to different treatment processes currently employed in Sweden and also variability in raw water, i.e. COD, alkalinity and N-NH_4^+ content (Table 1).

As API's begin to react with O_3, they are also competing with the matrix components of the effluent for O_3 degradation, therefore this study attempted to correlate the DO_3 with the effluent characteristics.

2. Materials and Methods

2.1 Chemicals

All pharmaceutical reference standards were of analytical grade (>98%) purchased from different suppliers (Table S3). A stock solution of the APIs was prepared in methanol (Merck, Darmstadt, Germany) at concentration of about 100 mg/L. The experimental set-up for the ozonation was based on a 1.0 g/h ozone generator from O_3-Technology AB,Vellinge, Sweden, which was supplied with dry oxygen gas. The generated O_3 was dispersed though a diffuser in a collection bottle containing Milli-Q water. The later one was immersed in an icebath sot that O_3 solubility is increased. Based on these experimental conditions, the concentration of O_3 in the stock solution was between 30 and 40 mg/L. Further details are found in Antoniou and Andersen (2012).

2.2 Wastewater effluents

Effluents from five WWTPs in Sweden, including Källby (Effluent 1&2), Björnstorp (Effluent 3), Oresundsverket (Effluent 4), Sjölunda (Effluent 5), and Nykvarnsverket

(Effluent 6) were used in this study. Effluent 1 and Effluent 2 were from the same treatment plant but were collected on separate occasions with a 3 week time interval. Although Effluent 1 and Effluent 2 come from the same WWTP, they were treated as 2 different effluents due to the variability of their characteristics. This difference is attributed to the significant rainfall events which occurred following the first sampling event. Continues rainfall most likely caused a sludge wash-out, reducing the biological treatment efficiency and increasing the COD value, while at the same time alkalinity value reduced because of dilution with the rain water. The characteristics and treatment processes that are performed at each WWTP are listed in Table 1 and extensively described in S.I., respectively. As nitrification was well functioning in all WWTPs, the measured concentration of nitrite in the effluents was below 0.1 mg/L.

Table 1. Source and characterization of the wastewater effluents.

WWTP	Källby 1	Källby 2	Björnstorp	Öresundsverket	Sjölunda	Nykvarnsverket
	Eff1	Eff2	Eff3	Eff4	Eff5	Eff6
COD, mg/L	29	51	30	36	90	44
DOC, mg/L	7.5	6.5	5.2	8.1	13.7	8.4
Alkalinity, mg HCO_3^-/L	244	154	185	229	256	164
pH	6.6	6.7	7.0	7.2	6.7	6.8
N-NH_4^+, mg/L	1.36	2.98	0.77	4.93	1.86	5.98
SUVA, (L/mg)/m	2.74	2.94	2.07	2.10	1.86	2.01
A254, cm^{-1}	0.206	0.190	0.107	0.171	0.256	0.168

2.3 Experimental set-up

Effluent was spiked with the APIs standard to give a nominal concentration of 1 µg/L, and then transferred into borosilicate glass vials, where different volumes of O_3 stock solution were added (in triplicate) to give nominal concentrations between 0.5 and <12 mg/L O_3 for a total volume of 150 mL. Vials were then placed in a covered waterbath at 15°C for at least 10 hours which is significantly more than the lifetime of O_3 in wastewater. The doses of O_3 delivered in each experiment varied (~5% relative standard deviation, RSD) since the concentration of O_3 in the stock solution was variable between days, but the delivered O_3 dose to the vials was quantified exactly by adding the same volume of ozone stock solution to vials prepared with indigo trisulfonate solutions as was added to the effluents. The loss of indigo trisulfonate is proportional to the O_3 mole to mole. Further details of the ozonation procedure and quantification is given in Antoniou and Andersen, 2012. Over several method evaluation performed in parallel to the experiments using each time several vials prepared with indigo trisulfonate solutions the repeatability of the added O_3 dose was always better than 5% RSD.

2.4 Analysis

DOC, pH, alkalinity (mg HCO_3^-/L), COD, and NH_4^+ concentrations in the effluent were quantified based on standard methods. UV-absorbance at 254 and 272 nm was measured before and after ozonation with a Varian CARY 50Bio UV-Vis spectrophotometer. Specific UV-absorbance (SUVA) was determined by dividing the sample absorbance at λ=254 nm with the corresponding DOC value. The specific O_3 dose delivered (DO_3) was measured with the colorimetric method of indigo (λ = 600nm), by preparing bottles with indigo trisulfonate solution in Milli-Q water in parallel with the treatment samples (Antoniou and Andersen, 2011; Bader and Hoigne, 1981). After SPE extraction, the APIs were quantified by LC/MS/MS using a triple-stage quadrupole mass spectrometer (MS/MS TSQ Quantum Ultra EMR) coupled to an Accela LC pump (both from Thermo Fisher Scientific, San Jose, CA, USA) and a PAL HTC autosampler (CTC Analytics AG, Zwingen, Switzerland) with a Hypersil GOLD aQ^{TM} column (50 mm x 2.1 mm ID x 5 μm particles). The same method was used to investigate the fate of APIs in wastewater treatment by Hörsing et al. (2011) and Hey et al. (2012) and a full method evaluation and detailed description is given in Grabic et al. (2012).

2.5 Data treatment

In order to determine the O_3 dose that achieved 90% removal of each API in every effluent, the removal rate achieved with each O_3 dose in each effluent were fitted with Equation 1. Equation 1 is an exponential formula that describes the remaining API concentration in relation to its initial concentration after a specific O_3 dose is delivered (DO_3). It is dependent on the fact that ozone's fate in the effluent is determined by the effluent's matrix and not significantly affected by the reaction with the APIs; therefore is independent from the APIs concentration. The equation contains the O_3 dose required to remove 90% of the API as a constant (here noted as decadic dose of O_3 DDO_3), allowing determination of the standard error directly through curve fitting. The fitted parameter is named the decadic dose of O_3, DDO_3.

$$(Eq.1) \qquad \log\left(\frac{C}{C_o}\right) = \frac{-DO_3}{DDO_3} \Leftrightarrow C = C_o \cdot 10^{-\left(\frac{DO_3}{DDO_3}\right)}$$

Equation 1 resembles the general formula used for the characterization of the effectiveness of energy intensive advanced treatment methods (Equation 2) recommended by IUPAC and described by Bolton et al. (2001). Equation 2 correlates the electrical energy dose (*EED*) with

the residual concentration of the treatment target compound and uses the constant E_{EO} which is the *EED* required to achieve 90% removal (Bolton et al., 2001).

$$(Eq.2) \qquad \log\left(\frac{C}{C_o}\right) = \frac{-EED}{E_{EO}}$$

Equation 1 was suggested by Hansen et al., (2010) who used both Equations 1 and 2 to describe the effectiveness of O_3 treatment for estrogenic chemicals in WWTP effluents in terms of the O_3 and energy dosage applied. Based on the above, it was decided to use the same system of equations to describe the effectiveness of O_3-treatment for API removal from wastewater. Data treatment (determination of DDO_3) was conducted in GraphPad Prism 5.

3. Results and Discussion

3.1 Removal of APIs from 6 WWTP effluents: Effect of wastewater matrix

In this study, 42 APIs commonly found in WWTP effluents in Sweden were spiked in six different WWTP effluents and treated with O_3 to evaluate their removal efficiencies and the effect of the matrix. Figure 1 summarizes the contribution of each O_3 dose (0.5 to ~12.0 mg/L O_3) on the removal of the APIs in each one of the six WWTP effluents. The order with which APIs appear in the *x*-axis is with declining order of percentage removal achieved with the lowest O_3 dose. The same data is also shown in Figure 2 (few examples) and Figures S1 to S6, but plotted in a less condensed manner allowing representation of experimental variation. A general trend can be seen whereby increasing O_3 dosage increases API removal efficiency (Figure 1). However, great variability is observed in required O_3 dose to achieve removal of different APIs within the same effluent and for the same API between effluents.

For the lowest delivered O_3 dose (0.5-0.6 mg/L), Effluent 1 and Effluent 3 had the highest number of APIs exhibiting removal efficiencies between 50-100%, possibly due to their low COD values compared to other effluents. Low COD values reduce the competition for O_3 between APIs and organic matter of the matrix required for degradation. The high alkalinity value observed in Effluent 1(highest in the group, Table 1) did not seem to significantly affect API removal. However, APIs in Effluent 5 appear to be the most recalcitrant to O_3 treatment, with all exhibiting <50% removal at the lowest delivered O_3 dosage. A significant increase in O_3 dosage to ~8.9 mg/L, had little effect on API removal in Effluent 5 compared to the other effluents, since only 18 out of 42 were removed by levels greater than 90%. It is believed that both high COD (~90 mg/L) and alkalinity (~250 mg HCO_3^-/L) levels present in Effluent 5 contributed to inhibiting the API removal.

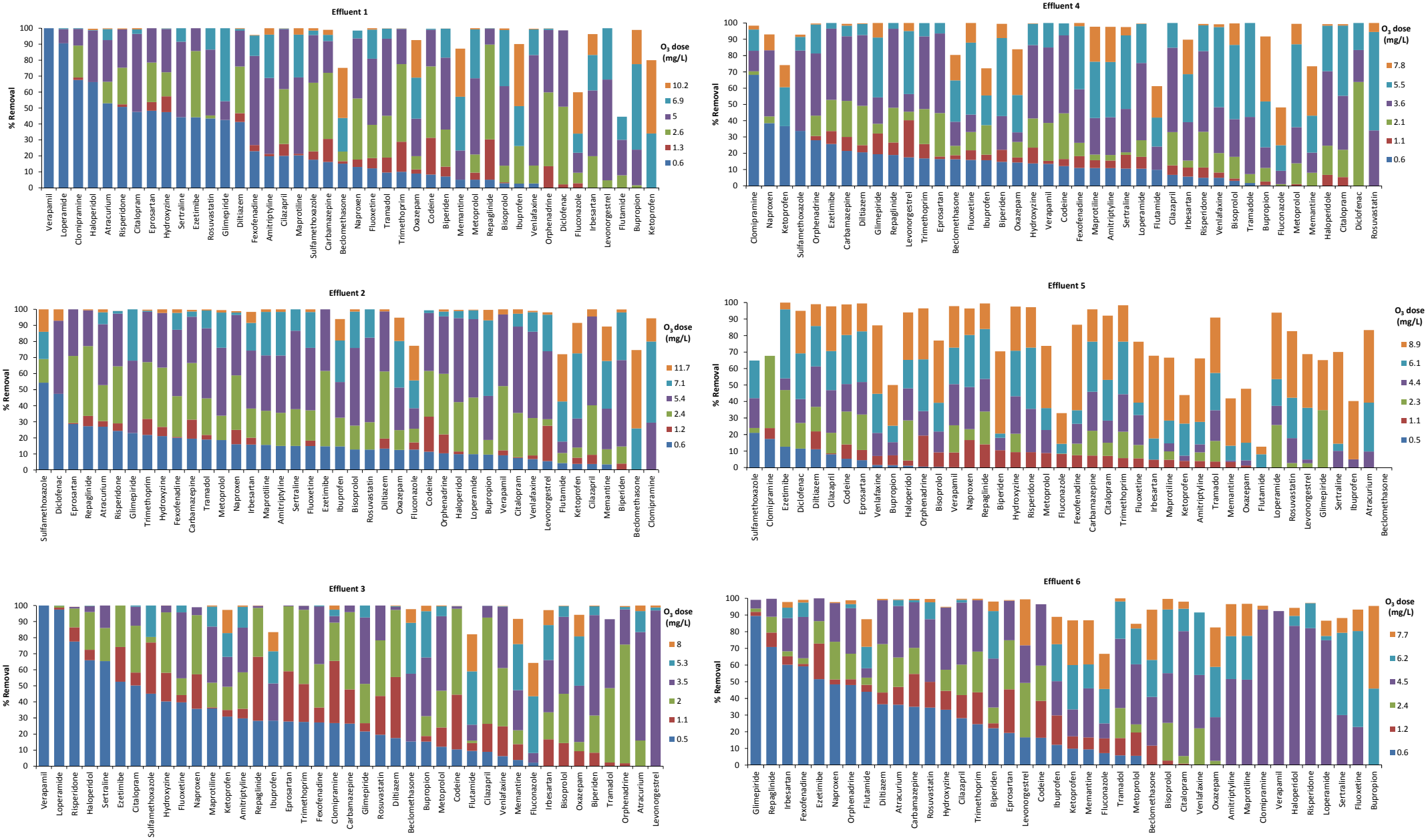
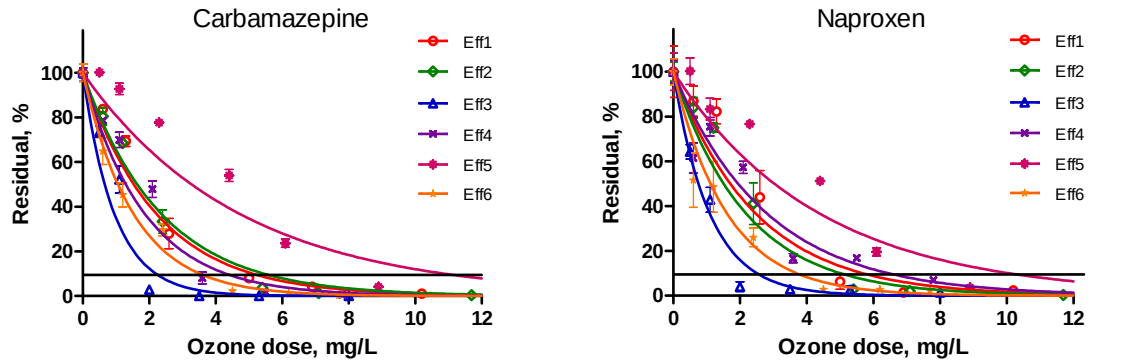


Figure 1: Profiles of dose dependency for the removal of pharmaceuticals in the 6 investigated wastewaters.

Overall, all APIs in Effluents 2, 3, and 6 were removed by over 50% at the highest O_3 dosage. In Effluents 1 and 4, only 1 API had less than 50% removal, while 7 APIs were poorly removed (< 50%) in Effluent 5 even at the highest O_3 dosage.

Based on the results shown in Figure 1, an APIs' susceptibility to O_3 degradation appears to be highly dependent on the type of wastewater used, explaining the wide range of removal efficiencies that some APIs exhibited in this study. Specifically, the synthetic steroid beclomethasone was removed between 0-98% in the 6 effluents. Removal of fluconazole (antifungal) and flutamide (antiandrogen) ranged between 33-77% and 13-87%, respectively, inferring that some APIs were not effectively degraded (to reach the treatment goal of 90%) in any of the tested- effluents with the applied O_3 doses.

A



B

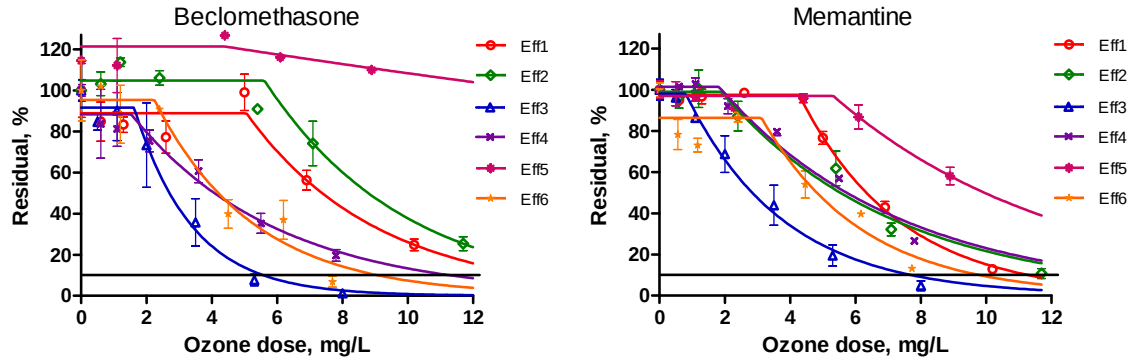


Figure 2: Concentration profiles for selected APIs in different WWTP effluents, which follow first order decay with the delivered O_3 dose (DO_3) (**A**) or exhibiting an apparent lag-phase (**B**). The intersect of the black horizontal line with the 10 % remaining API concentration (*y*-axis) indicates the corresponding DDO_3. T-bar represent standard deviation with n=3.

3.2 Required ozone dose to achieve 90% removal of API in WWTP effluents

In order to determine the O_3 dosage that achieving 90% removal of each API in every effluent, the data shown on Figure 1 were fitted with Equation 1. For each API and effluent there are 3 results of each O_3 dose applied that stems from the triplicate O_3 addition which are fitted as independant points. Selected fitting curves are shown in Figure 2 and all the curves for the 42 APIs in the 6 effluents are shown in Figures S1-S6.

In this study, at lower O_3 doses an apparent lag-phase towards degradation was observed for some APIs and it wasn't until higher O_3 doses were applied that degradation occurred (Figure 2B). Once the O_3 lag-phase dose was surpassed, a decrease of APIs concentrations was observed as DO_3 increased which is similar to the curve shape (exponential decay) for APIs which did not show this lagphase. It is our belief, that the lag-phase is a result of the low reactivity of some APIs for direct reaction with O_3 in addition to the competition with the wastewater matrix for O_3 degradation. Some of the matrix components react directly with O_3 and quickly consume the low O_3 doses, therefore reducing the chances of O_3 reacting with the target compounds. It is only when O_3 is added at higher doses than required to satisfy the O_3 reactive part of the matrix, that enough O_3 remains for the recalcitrant APIs to be degraded either directly or through the secondary pathway which is mediated by $HO^{\bullet}$ ($O_3 + H_2O \rightarrow 2HO^{\bullet} + O_2$), assuming O_3 remains in the wastewater long enough to convert to the radical form. To fit the concentration curves of APIs that showed apparent lag of reactivity towards low O_3 doses, a variation of Equation 1 was developed and shown as Equation 3 (see Figure S7 for graphical representation).

$$(Eq.3) \qquad IF: DO_3 < LagO_3 \rightarrow C = C_o$$

$$IF: DO_3 > LagO_3 \rightarrow C = C_o \cdot 10^{-\left(\frac{DO_3 - LagO_3}{D}\right)}; \qquad DDO_3 = D + LagO_3$$

The resulting estimated DDO_3 values of each API in all the effluents are presented in Table 2. Significant variation is observed in the DDO_3 values of a specific API depending on the wastewater effluent matrix. For example, carbamazepine exhibited a low DDO_3 of ~2 mg/L in Effluent 3, compared to the high DDO_3 of ~ 10 mg/L in Effluent 5. This confirms the strong influence exerted by the wastewater matrix components on APIs removal efficiencies with O_3. This has also been observed by Benitez et al. (2009) during O_3-treatment of pharmaceuticals (including metoprolol and naproxen) in surface and ground water and wastewater. Their results showed higher pharmaceutical removal in surface water (alkalinity=30 mg $CaCO_3$/L) compared to groundwater (alkalinity=388 mg $CaCO_3$/L), while

Table 2: Ozone dose for removal of the first decade of each pharmaceutical in each wastewater and the dose relative to the DOC . (NA* = compound not quantified due to chromatographic shift of peak outside of the MS window; NA** = out of range, either <<lowest dose or >> highest dose of ozone applied)

	DDO_3 (ppm O_3)						[DDO_3/DOC]						
API	Eff1	Eff2	Eff3	Eff4	Eff5	Eff6	Eff1	Eff2	Eff3	Eff4	Eff5	Eff6	**Ave**
						Easily degradable							
Repaglinide	2.6	3.7	1.8	4.1	8.7	1.5	0.35	0.57	0.35	0.50	0.64	0.18	**0.43**
Ezetimibe	3.2	4.6	1.5	3.8	8.0	2.0	0.43	0.71	0.29	0.47	0.58	0.24	**0.45**
Diltiazem	3.6	3.7	2.2	4.3	8.0	3.9	0.48	0.57	0.42	0.53	0.58	0.47	**0.51**
Eprosartan	3.2	4.9	1.9	4.5	9.1	4.2	0.43	0.76	0.37	0.55	0.66	0.50	**0.55**
Trimethoprim	4.0	4.3	2.1	4.4	9.7	3.9	0.53	0.67	0.40	0.54	0.71	0.47	**0.55**
Clomipramine	2.3	7.3	2.4	3.7	7.5	4.2	0.31	1.13	0.46	0.45	0.55	0.50	**0.57**
Risperidone	3.5	4.7	0.9	5.5	12.1	5.0	0.47	0.73	0.17	0.68	0.88	0.60	**0.59**
Hydroxyzine	3.4	5.7	1.9	4.8	10	4.8	0.45	0.88	0.37	0.59	0.73	0.57	**0.60**
Codeine	4.2	4.9	2.4	4.6	9.2	5.4	0.56	0.76	0.46	0.57	0.67	0.65	**0.61**
Carbamazepine	5.1	5.4	2.2	4.3	10.8	3.5	0.68	0.84	0.42	0.53	0.79	0.42	**0.61**
Naproxen	5.7	5.0	2.5	6.4	10	3.7	0.76	0.77	0.48	0.79	0.73	0.44	**0.66**
Fexofenadine	5.2	5.8	3.0	6.5	9.1	2.9	0.69	0.90	0.58	0.80	0.66	0.35	**0.66**
Orphenadrine	4.5	5.0	3.4	4.8	12.1	4.0	0.60	0.77	0.65	0.59	0.88	0.48	**0.66**
Diclofenac	4.7	5.8	NA*	3.5	10	NA*	0.63	0.90	NA*	0.43	0.73	NA*	**0.67**
Cilazapril	4.5	7.1	2.7	5.7	11	4.0	0.60	1.10	0.52	0.70	0.80	0.48	**0.70**
						Moderately degradable							
Loperamide	2.0	4.5	<0.5	5.7	13.3	8.7	0.27	0.70	NA**	0.70	0.97	1.04	**0.74**
Glimepiride	7.0	7.6	3.6	6.7	>>8.9	0.6	0.93	1.18	0.69	0.82	NA**	0.07	**0.74**
Rosuvastatin	5.4	5.6	3.3	5	14.5	4.8	0.72	0.87	0.63	0.61	1.06	0.57	**0.74**
Haloperidole	4.8	7.8	1.5	6.3	11.8	5.9	0.64	1.21	0.29	0.77	0.86	0.71	**0.75**
Sulfamethoxazole	4.8	4.5	3.6	4.5	17.6	NA*	0.64	0.70	0.69	0.55	1.28	NA*	**0.77**
Verapamil	NA*	5.4	<0.5	5.0	10.5	7.5	NA*	0.84	NA**	0.61	0.77	0.90	**0.78**
Tramadole	5.7	5.8	3.4	6.3	13	6.4	0.76	0.90	0.65	0.77	0.95	0.77	**0.80**
Citalopram	5.0	7.8	2.0	7.1	15	5.0	0.67	1.21	0.38	0.87	1.09	0.60	**0.80**
Sertraline	6.4	5.2	1.7	7.9	12	11.6	0.85	0.81	0.33	0.97	0.88	1.39	**0.87**
Venlafaxine	5.3	6.3	3.4	6.4	16.6	9.3	0.71	0.98	0.65	0.79	1.21	1.11	**0.91**
Maprotiline	7.3	6.9	4.1	8.3	13.6	7.2	0.97	1.07	0.79	1.02	0.99	0.86	**0.95**
Bisoprolol	7.2	6.0	3.3	7.3	21	7.2	0.96	0.93	0.63	0.90	1.53	0.86	**0.97**
Amitriptyline	7.3	9.4	3.6	8.3	13.6	7.3	0.97	1.46	0.69	1.02	0.99	0.87	**1.00**
Metoprolol	6.9	6.9	3.8	7.4	18.2	8.8	0.92	1.07	0.73	0.91	1.33	1.05	**1.00**
Biperiden	5.9	6.3	4.3	7.3	23	7.4	0.78	0.98	0.83	0.90	1.68	0.88	**1.01**
Levonorgestrel	6.7	7.3	6.6	6.0	18.2	6.5	0.89	1.13	1.27	0.74	1.33	0.78	**1.02**
Fluoxetine	6.6	6.8	3.1	7.7	20	11.3	0.88	1.05	0.60	0.95	1.46	1.35	**1.05**
Irbesartan	8.7	7.7	5.4	11.5	13.7	4.3	1.16	1.19	1.04	1.41	1.00	0.51	**1.05**
Bupropion	8.1	8.0	5.2	9.3	>>8.9	12.1	1.08	1.24	1.00	1.14	NA**	1.45	**1.18**
						Recalcitrant towards ozone degradation							
Oxazepam	12.3	11.3	7.1	13.5	18.4	9.7	1.64	1.75	1.37	1.66	1.34	1.16	**1.49**
Ketoprofen	13.4	12.7	5.5	13.2	23.9	9.7	1.78	1.97	1.06	1.62	1.74	1.16	**1.56**
Memantine	11.4	12.8	7.8	14.5	21.3	10.2	1.52	1.98	1.50	1.78	1.55	1.22	**1.59**
Ibuprofen	11.5	10.9	7.3	14.7	27	10.4	1.53	1.69	1.40	1.81	1.97	1.24	**1.61**
Beclomethasone	20	18	5.8	12	>>8.9	9.2	2.66	2.79	1.12	1.47	NA**	1.10	**1.83**
Atracurium	3.7	6.2	4.4	11	11.1	3.9	0.49	3.13	0.85	1.35	0.81	0.47	**1.18**
Flutamide	>>10.2	25	11.7	17.9	>>8.9	9.4	NA**	3.87	2.25	2.20	NA**	1.12	**2.36**
Fluconazole	15.1	18	10.7	20	>>8.9	22	2.01	2.79	2.06	2.46	NA**	2.63	**2.39**

the effluent containing the lowest DOC and alkalinity had the highest removal among the 3 secondary effluents tested (Benitez et al., 2009).

Based on the above, and in order to categorize the different pharmaceuticals into easily degradable, moderately degradable and recalcitrant towards O_3 degradation, the Specific DDO_3 value was calculated. Specific DDO_3 is calculated by dividing the DDO_3 by the effluent DOC [DDO_3/DOC]. The selection criterion for an API to be characterized as easily degraded was decided to be a [DDO_3/DOC] value of ≤ 0.7. Fifteen out of 42 investigated APIs fulfilled this criterion including repaglinide (antidiabetic), trimethoprim (antibiotic), carbamazepine (antiepileptic) and diclofenac (antiphlogistic) and naproxen (antiphlogistics). Nineteen APIs fulfilled the moderately degradable criterion of $0.7 < [DDO_3/DOC] \leq 1.4$ including sulfamethoxazole (antibiotic), metoprolol and bisoprolol (beta blockers) and citalopram, amitriptyline, maprotiline, venlafaxine, fluoxetine, bupropion and sertraline (antidepressants). The remaining 8 APIs, such as beclomethasone and the antiphlogistics ketoprofen and ibuprofen, were considered O_3-recalcitrant since they had [DDO_3/DOC] >1.4.

Previous studies of the cited literature (Hollender et al. 2009; Bahr et al.,2010) have also used the O_3 dose in relation to the DOC wastewater value to describe the treatment efficiency. In a study conducted by Hollender et al. (2009) on the removal of organic micropollutants from wastewater with O_3, which included 24 pharmaceuticals, the fast reacting APIs sulfamethoxazole, diclofenac, carbamazepine and trimethoprim were eliminated at a dose of 0.47 g O_3/g DOC (dissolved organic carbon). In our study we found that the same compounds require from 0.55 up to 0.77 g O_3/g DOC for 90% removal. Furthermore, Bahr et al., (2010) reported complete removal of naproxen, diclofenac and carbamazepine at a specific ozone dose of 0.5 g O_3/g DOC during ozonation of secondary WWTP effluent. Our study predicts the dosage required for 90 % removal of these APIs to be in the order of 0.61-0.66 g O_3/g DOC. While for slow reacting compounds, such as ibuprofen and ketoprofen, a specific ozone dose > 1 g O_3/g DOC is required for > 95% removal according to Bahr et al., 2010. In comparison, our work showed the dosage of ozone required for 90 % removal to be 1.61 and 1.51 g O_3/g DOC, respectively, for these two APIs.

The degradation profiles of select APIs in the 6 effluents that follow first order decay with the added O_3 (carbamazepine, naproxen) are shown in Figure 2A while Figure 2B depicts the degradation profiles of the APIs that exhibited an apparent lag phase before any significant degradation occurred (beclomethasone, memantine). Intersection of the horizontal line with the *y*-axis in Figures 2 and S1-S6 indicates the DDO_3 of the APIs from which it is

evident that Effluent 5 is the most recalcitrant to O_3-treatment as it requires the higher DDO_3 for all APIs compared to the other effluents (Figures 2A and 2B).

Based on the data shown in Table 2, the average [DDO_3/DOC] for the majority of the APIs is ≤ 1.2, while only a few exhibit a [DDO_3/DOC] > 1.5. Thus, an O_3 dose of 1.4 g per g DOC should be sufficient to remove (by at least 90%) more than 80% of the APIs tested in this study. However, in order to remove the most O_3-recalcitrant APIs as well, a twice as high O_3 dose ([DDO_3/DOC]> 2.4 g O_3 per g DOC) is needed which results in a significantly more costly treatment process.

3.3 Effect of chemical structure of APIs on O_3 reactivity

The chemical structure of each API and the functional groups comprising it determine whether an API would be easy or difficult to degrade with O_3. Due to its electronic configuration, O_3 can perform different types of reactions in water including oxidation reactions, cycloadditions and electrophilic substitution reactions (Beltrán, 2004). Easily degradable APIs (relatively low [DDO_3/DOC] values) are characterized by the presence of electron-rich functional groups and they mainly react readily with O_3 through electrophilic substitution. These functional groups include C=C double bonds (found in eprosartan, carbamazepine), tertiary amines (repaglinide, clomipramine), aniline (dicofenac), phenol (iezetimibe) and methoxy groups (trimethoprim, diltiazem, naproxen) (Hoigne and Bader, 1976; Huber et al., 2003; Huber et al., 2005; Nakada et al., 2007, Hollender et al., 2009).

APIs which are poorly removed (relatively high [DDO_3/DOC] values) generally contain electron-withdrawing functional groups, such as fluoro (flutamide, fluconazole), nitro (flutamide), chloro (beclomethasone), amide (flutamide) and carboxyl (ibuprofen, ketoprofen) (Hey et al., 2012; Nakada et al., 2007; Acero et al., 2000; Hollender et al., 2011). Electron withdrawing groups reduce e^- density from the APIs structure inhibiting electrophilic substitution reactions from occurring. In addition, the electronegative groups themselves are less likely to react with O_3 and thus cause a shielding effect.

Some easily degradable APIs such as carbamazepine and diclofenac also contain electron-withdrawing functional groups (amide in carbamazepine, chloro and carboxylic acid in diclofenac) but remain O_3-reactive, inferring the presence and position of the high e-density functional groups, such as the aromatic amine (diclofenac) and C=C double bond (carbamazepine) (Nakada et al., 2007), counteracts the inhibitory effect .

Ibuprofen possesses no electron-rich functional group and is recalcitrant towards O_3-treatment (Huber et al., 2005) however can be adequately removed through intense biological treatment (e.g. (Fick et al., 2011; Falås et al., 2012a, 2012b)). In addition, effective oxidative removal of O_3-resistant APIs may be possible through the hydroxyl radical pathway (Antoniou et al., 2008).

4. Conclusions

- When the effect of O_3 dose on degradation of 42 APIs in 6 different WWTP effluents was investigated, a large variability between APIs and effluents types was observed.
- The estimated DDO_3 of a specific API, used to evaluate the necessary O_3 dose to achieve reduction by one decade, varied significantly among the effluents investigated.
- DDO_3 was correlated with the effluent DOC by calculating the DDO_3/DOC for each API in every effluent. This enabled ranking of the different APIs into easily degradable, moderately degradable and recalcitrant to O_3-treatment categories.
- Following this practice, the required O_3 dose can be predicted based on the target pharmaceutical and the matrix component of the wastewater (DOC) to be treated.
- An O_3 dose of 1.4 g per g DOC removed (by at least 90%) more than 80% of the APIs tested in this study. To remove the most O_3-recalcitrant APIs a dose in the order of 2.4 g O_3 per g DOC is required.

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